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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,734	07/14/2003	Gregory Gregoriadis	G0365.0365/P0365	3606

7590 06/13/2006

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/617,734	GREGORIADIS, GREGORY	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6-20,22,25-31 and 34-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6-20,22,25-31 and 34-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. 09/254,695.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 3/28/06.

Claims 2, 4, 5, 21, 23, 24, 32, and 33 were canceled and claim 38 was added.

Claims 1, 3, 6-20, 22, 25-31, and 34-38 are pending and under consideration in this Office Action.

Rejections Withdrawn

After further consideration the indefiniteness rejection of claims 6-8 is withdrawn. It would be clear to those of skill in the art what was intended by "the intravesicular space".

Applicant's amendments overcame the indefiniteness rejection of claims 34-37.

Applicant's amendment overcame the enablement rejection of claim 35.

Applicant's amendments necessitated new grounds of rejection under 35 USC 103 for all claims.

Claim Objections

Claim 6 is objected to because it was amended by insertion of the word "an" immediately preceding "aqueous", but its status is identified as "(Original)" instead of "(Currently Amended)". See 37 CFR 1.121 which sets for the proper manner of making amendments to the claims, and requires the use of the proper status identifiers.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-20, 22, 25-32 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 17-20, 22, 25-32 indefinite because claim 17 recites "formed from liposome selected from the group consisting of lipids, cholesterol and non-ionic and cationic surface active agents". None of "lipids, cholesterol and non-ionic and cationic surface active agents" is a liposome. These are liposome-forming agents. The metes and bounds of the claim are also unknown because it is unclear to what the phrase "present in an amount whereby the small unilamellar vesicles have an overall cationic charge" should be applied. This could be applicable only to "cationic surface agents" or it could be applicable to "cationically charged components". Claim 17 also recites "the intravesicular space thereof" without proper antecedent basis.

Applicant did not respond to this ground of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6, 8-14, 16-20, 25-31, and 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent 5,264,618) in view of and Kirby et al (Bio/Technology (1984), 2(11), 979-84) and Weiner (US Patent 5,593,972, filed 9/21/93).

Felgner taught methods of inducing an immune response in an animal by delivering compositions comprising cationic liposomes encapsulating polynucleotides that encode immunogens. See abstract; column 4 line 68 to column 5, line 24; paragraph bridging columns 6 and 7; column 7, lines 39, 40, and 49-56; paragraph bridging columns 7 and 8; particularly column 8, lines 3, 4, 7, and 21-31; column 15, lines 7-25; paragraph bridging columns 17 and 18; and column 18, lines 30-53. The cationic liposomes comprise DOTAP, phosphatidylethanolamine, and dioleoylphosphatidyl-choline, and lipids of the general structures disclosed in claims 9, 10, 26, and 27. See for example paragraph bridging columns 13 and 14; and column 14, lines 37-46. Because Felgner taught that DNA encoding a polypeptide could be delivered to a cell for expression, Felgner is considered to fairly teach double stranded DNA since single stranded DNA is not expressed. Felgner taught delivery of mRNA at column 18, lines 12-18. Administration routes include intramuscular and subcutaneous. See column 20, lines 31-38 and column 22, lines 5-8. Felgner also taught liposomes having a net positive charge. See paragraph bridging columns 14 and 15.

Felgner did not teach liposomes having diameters in the range of 100-2000 nanometers, a dehydration rehydration method of liposome synthesis, or a plasmid comprising a promoter and encoding an immunogen, or an antigen of a microbe,

Kirby taught a dehydration-rehydration method of encapsulating solutes such as DNA into liposomes. See abstract and Table 1 on page 980. Kirby also taught liposomes comprising a cationically charged component, a non-ionic component and a zwitterionic ionic component, wherein the cationic component (stearylamine) was present at 10 mol% and conferred a positive charge on the liposomes. See Table 1 on page 980; and page 983, column 2, first sentence of second full paragraph. For DNA encapsulation, the DNA was mixed with empty, small unilamellar vesicles, the mixture was lyophilized, and subsequently rehydrated to form dehydration rehydration vesicles encapsulating DNA. See e.g. paragraph bridging columns 1 and 2 on page 983. Encapsulation efficiency of DNA was 72% +/- 8.5%. See Table 1. Vesicles made by this dehydration rehydration process averaged 0.30+/-0.28 microns in diameter, with a maximum size of 2 microns, and 95% of the particles being less than 1 micron. See page 982, column 2, lines 5-10. Kirby also taught a composition comprising 0.1-10 micrograms polynucleotide to mg of liposome-forming components (instant claim 14). See specification at page 15, lines 14-33, referencing Kirby at lines 14 and 28. This passage discloses incorporation in this range by mixing 16 micromoles of lipid with from 10-100 micrograms of DNA, and then performing the dehydration-rehydration procedure. Similarly, Kirby taught the formation of liposomes by addition of 8.25 micromoles of phospholipids with 50 micrograms of DNA. See Table 1 on page 980 which teaches that DNA was used at a concentration of 100 micrograms per ml, and that phospholipids were used at a concentration of 16.5 micromoles per ml; and page 983, column 2, lines 1-5 which disclose that lipids and material to be entrapped were

combined in equal volumes of 0.5 ml each. Kirby also taught a separate step of separating unincorporated materials from liposomes. See page 983, column 2, lines 16-22. In view of the 72% in corporation efficiency achieved by Kirby, about 18% of the polynucleotide would be expected to be entrapped and removed by the separation step.

Weiner taught methods of causing an immune response in an individual by injection of a polynucleotide encoding an immunogen. In one embodiment the polynucleotide is a plasmid comprising a promoter and administered in a complex with a liposome. See column 1, lines 14-19; column 9, line 53 to column 10, line 8; column 10, lines 59-65; column 12, lines 6-13; and column 20, lines 37-39. Alternatively the polynucleotide is mRNA. See column 11, lines 23-28. The immunogenic polypeptide comprises an antigen of an infectious virus, such as HIV, influenza virus, hepatitis B virus and hepatitis C virus, or an antigen of a hyperproliferative cell associated with a hyperproliferative disease. See column 13, lines 5-13; column 14, lines 6-14; column 52, line 62 to column 56, line 21; and claims 1-7, columns 69 and 70. Weiner also discloses use of Hepatitis B virus surface antigen as an immunogen. See e.g. column 2, lines 55-60. The polynucleotide can be administered intramuscularly, or subcutaneously. See paragraphs bridging columns 16 and 17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the dehydration-rehydration method of Kirby to encapsulate DNA in liposomes for use in the method of Felgner. One would have been motivated to do so because the method of Kirby is a simple method which provides excellent encapsulation yields while using mild conditions. See title, page 979; column 1, lines 5-8 of second

paragraph; and Table I on page 980. Also the method results in a greater proportion of oligo- and multilamellar vesicles which decrease the rate of loss of entrapped solutes (see paragraph bridging pages 982, and 983) and would be expected to exclude nucleases with greater success than unilamellar vesicles, thereby increasing the stability of the encapsulated nucleic acid.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the polynucleotides of Weiner in the invention of Felgner as modified by Kirby. One would have been motivated to do so because both Felgner and Weiner suggest that liposomal compositions should be used for *in vivo* delivery of nucleic acids encoding immunogens.

Although the cited references are silent as to whether the stimulated immune response would involve both an IgG response and Th1 and Th2 responses, the cited art teaches all the required method steps, and the result is considered to be inherent in the steps. The masses of DNA and liposome-forming components used are routinely optimized and are considered to be obvious. See MPEP 2144.05 IIA.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent 5,264,618), Kirby et al (Bio/Technology (1984), 2(11), 979-84) and Weiner (US Patent 5,593,972, filed 9/21/93) as applied to claims 1, 2, 6, 8-14, 16-20, 25-31, and 34-38 above, and further in view of Collins (US Patent 5,567,433).

The teachings of Felgner, Kirby, and Weiner are summarized above and can be combined to render obvious methods of inducing an immune response in an animal by

administering intramuscularly or subcutaneously aqueous suspensions of cationic liposomes in the range of 100-2000 nm in diameter, wherein the liposomes encapsulate in their intravesicular spaces nucleic acids comprising a promoter and encoding an antigen of an infectious microbe. The references also render obvious a means of making the liposomes by a dehydration-rehydration technique as in instant claims 6 and 8.

The cited references do not teach microfluidization of liposomes.

Collins taught that microfluidization enhances the scale-up of liposome production. See column 6, lines 3-21. Collins also taught a method of making dehydration-rehydration cationic liposomes for the purpose of encapsulating nucleic acids. See paragraph bridging columns 4 and 5, and column 5, lines 3-21.

It would have been obvious to one of ordinary skill in the art at the time of the invention to microfluidize the liposomes resulting form the combination of the Felgner, Kirby, and Weiner references, as taught by Collins because microfluidization enhances the scale-up of liposome production, as noted above, thereby allowing production of greater amounts of vaccine.

Claims 1, 3, 6, 8-14, 16-20, 22, 25-31, 34, 35, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Felgner et al (US Patent 5,264,618) in view of and Kirby et al (Bio/Technology (1984), 2(11), 979-84) and Liu et al (WO 95/24485).

Felgner taught methods of inducing an immune response in an animal by delivering compositions comprising cationic liposomes encapsulating polynucleotides that encode immunogens. See abstract; column 4 line 68 to column 5, line 24; paragraph bridging columns 6 and 7; column 7, lines 39, 40, and 49-56; paragraph bridging columns 7 and 8; particularly column 8, lines 3, 4, 7, and 21-31; column 15, lines 7-25; paragraph bridging columns 17 and 18; and column 18, lines 30-53. The cationic liposomes comprise DOTAP, phosphatidylethanolamine, and dioleoylphosphatidyl-choline, and lipids of the general structures disclosed in claims 9, 10, 26, and 27. See for example paragraph bridging columns 13 and 14; and column 14, lines 37-46. Because Felgner taught that DNA encoding a polypeptide could be delivered to a cell for expression, Felgner is considered to fairly teach double stranded DNA since single stranded DNA is not expressed. Felgner taught delivery of mRNA at column 18, lines 12-18. Administration routes include intramuscular and subcutaneous. See column 20, lines 31-38 and column 22, lines 5-8. Felgner also taught liposomes having a net positive charge. See paragraph bridging columns 14 and 15.

Felgner did not teach liposomes having diameters in the range of 100-2000 nanometers, a dehydration rehydration method of liposome synthesis, or a plasmid comprising a promoter and encoding an immunogen, or an antigen of a microbe,

Kirby taught a dehydration-rehydration method of encapsulating solutes such as DNA into liposomes. See abstract and Table 1 on page 980. Kirby also taught liposomes comprising a cationically charged component, a non-ionic component and a zwitterionic ionic component, wherein the cationic component (stearylamine) was

present at 10 mol% and conferred a positive charge on the liposomes. See Table 1 on page 980; and page 983, column 2, first sentence of second full paragraph. For DNA encapsulation, the DNA was mixed with empty, small unilamellar vesicles, the mixture was lyophilized, and subsequently rehydrated to form dehydration rehydration vesicles encapsulating DNA. See e.g. paragraph bridging columns 1 and 2 on page 983. Encapsulation efficiency of DNA was 72% +/- 8.5%. See Table 1. Vesicles made by this dehydration rehydration process averaged 0.30+/-0.28 microns in diameter, with a maximum size of 2 microns, and 95% of the particles being less than 1 micron. See page 982, column 2, lines 5-10. Kirby also taught a composition comprising 0.1-10 micrograms polynucleotide to mg of liposome-forming components (instant claim 14). See specification at page 15, lines 14-33, referencing Kirby at lines 14 and 28. This passage discloses incorporation in this range by mixing 16 micromoles of lipid with from 10-100 micrograms of DNA, and then performing the dehydration-rehydration procedure. Similarly, Kirby taught the formation of liposomes by addition of 8.25 micromoles of phospholipids with 50 micrograms of DNA. See Table 1 on page 980 which teaches that DNA was used at a concentration of 100 micrograms per ml, and that phospholipids were used at a concentration of 16.5 micromoles per ml; and page 983, column 2, lines 1-5 which disclose that lipids and material to be entrapped were combined in equal volumes of 0.5 ml each. Kirby also taught a separate step of separating unincorporated materials from liposomes. See page 983, column 2, lines 16-22. In view of the 72% in corporation efficiency achieved by Kirby, about 18% of the polynucleotide would be expected to be entrapped and removed by the separation step.

Liu taught methods of causing an immune response in an individual by injection of a expression plasmids encoding two or more HIV antigens, wherein the immunogen coding sequences are linked by internal ribosome entry sites. The polynucleotide is be administered intramuscularly. The vaccines provide both cellular and humoral immunity. See abstract; paragraph bridging pages 9 and 10; page 20, line 3 to page 22, line 29; page 23, lines 1-4, page 51, lines 5-13, and paragraph bridging pages 52 and 53.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the dehydration-rehydration method of Kirby to encapsulate DNA in liposomes for use in the method of Felgner. One would have been motivated to do so because the method of Kirby is a simple method which provides excellent encapsulation yields while using mild conditions. See title, page 979; column 1, lines 5-8 of second paragraph; and Table I on page 980. Also the method results in a greater proportion of oligo- and multilamellar vesicles which decrease the rate of loss of entrapped solutes (see paragraph bridging pages 982, and 983) and would be expected to exclude nucleases with greater success than unilamellar vesicles, thereby increasing the stability of the encapsulated nucleic acid.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the polynucleotides of Liu in the invention of Felgner as modified by Kirby. One would have been motivated to do so because both Felgner and Weiner suggest that liposomal compositions should be used for *in vivo* delivery of nucleic acids encoding immunogens.

Although the cited references are silent as to whether the stimulated immune response would involve both an IgG response and Th1 and Th2 responses, the cited art teaches all the required method steps, and the result is considered to be inherent in the steps. The masses of DNA and liposome-forming components used are routinely optimized and are considered to be obvious. See MPEP 2144.05 IIA.

Response to Arguments

Applicant's arguments filed 3/28/06 have been fully considered as they might apply to the new grounds of rejection set forth above but they are not persuasive.

Applicant reviews the Felgner reference at pages 10-11 of the response, and concludes that there is no teaching or suggestion in Felgner of cationic liposomes in which polynucleotides are entrapped in the intravesicular space. The Examiner disagrees. The reference need not disclose applicant's invention in one sentence or even in one paragraph. The reference must be considered as a whole to determine what it fairly teaches. Felgner clearly states that the invention embraces delivery of nucleic acids that express immunogens in the paragraph bridging columns 7 and 8. Felgner also clearly indicates that therapeutic agents and "biologically active agents" include polynucleotides that can express proteins (see e.g. column 7, lines 49-56 and column 8, lines 60-65). Further, Felgner clearly teaches that the lipids of the invention may be used to form liposomes, and that the liposomes may encapsulate bioactive agents. See column 15, lines 7-25. There is no reason at all to assume that these active agents do include nucleic acids encoding immunogens.

Applicant asserts that Felgner teaches no in vivo results, however Applicant does not set forth any analysis that would lead one to the conclusion that the disclosure of Felgner was not enabling for the induction of an immune response. Furthermore, the Weiner and Liu references provide ample teachings to support this enablement.

Regarding the Collins reference, Applicant disagrees that the Collins teaches a method of making dehydration rehydration cationic liposomes for the purpose of encapsulating nucleic acids. However, in the rejection, Collins is relied upon for the teaching that microfluidization of liposomes enhances the scale-up of liposome production. There is nothing in Collins that suggests that microfluidization would not be applicable to the liposomes of Felgner, so one of ordinary skill in the art would reasonably expect to obtain the benefits of microfluidization when applying the process to these liposomes for the purpose of producing greater amounts of vaccine. For these reasons the rejections are considered proper.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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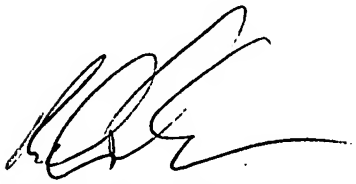

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Art Unit 1635